Biomarker for the Association between Body Mass Index and Lipid Peroxidation in T2DM with and without Microvascular Problems

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ABSTRACT

Obesity, diabetes, and the long-term effects of these conditions are all associated with increases in biomarkers. The rising rates of diabetes and cardiovascular disease as a result of the obesity pandemic have made it all the more important to investigate the potential use of inflammatory biomarkers generated by adipose tissue in high-risk individuals. Regrettably, no conclusive data supports the use of inflammatory indicators as a therapeutic intervention for people in transition at this time. In view of the therapeutic importance of temporary connections between biomarker elevations and various stages of type 2 diabetes, the current research seeks to address this question. Recent research has revealed that low-grade inflammatory biomarkers like EN-RAGE and IL-13 may be used to predict who will develop prediabetes and who will go on to develop diabetes. Biomarker tumour necrosis factor alpha (TNF-alpha) has been proposed to track the development of albuminuria as a chronic complication of type 2 diabetes. Cardiac biomarkers may serve as predictors of cardiac events in people with diabetes. Nonetheless, several linkages between biomarkers have been proposed as prospective techniques for identifying T2DM.

KEYWORDS: Biomarkers; Insulin Resistance; Inflammation; Overweight; Heart Disease; Blood Test Results

INTRODUCTION

There is growing evidence linking chronic inflammation to metabolic illnesses like diabetes, especially type 2 diabetes, and this has prompted some doctors to make educated guesses regarding the treatment implications of this discovery (T2DM). Many inflammatory indicators have been hypothesised to be involved in the transition from glycaemic control to what was once classified as type 2 diabetes. Newly diagnosed diabetics have been demonstrated to have elevated levels of many markers of low-grade inflammation [1]. This study aims to better understand the short-term treatment relevance of associations between biomarker increases and certain stages of type 2 diabetes. As a result, EN-RAGE (also known as S100A12 or Calgranulin C) has now been offered as a potential candidate for a pre-diabetes inflammatory marker [2]. Consensus exists that elevated EN-RAGE levels predict the likelihood that normoglycemia may proceed to prediabetes. In contrast with what was previously believed about high IL-13 levels, high EN-RAGE tiers are revealed to be related with an increased likelihood of developing pre-diabetes [3]. To this end, we analyse the biomarkers' responses as a possible predictor of T2DM's onset, progression, and long-term complications.

Type 2 diabetes mellitus is characterised by hyperglycemia, significant alterations in carbohydrates, amino, and lipid metabolism due to insulin insufficiency or decreased insulin action, and increased free radical activity (T2DM). There are now about 347 million people in the globe who have T2DM (Brussels, 2011; WHO), and this figure is continually increasing. Type 2 diabetes is associated with alterations in lipid profiles, such as an increased susceptibility for lipid peroxidation (Giugliano et al., 1996). It has been proven that oxidative stress is made worse in diabetics due to their increased production of free radicals (Seghrouchni et al., 2002). Free radical generating activities such as advanced glycosylated final product synthesis, protein glycation, glucose autoxidation, and activation of the polyol pathway cause oxidative stress in many tissues (Atalay et al.,

2002). Oxidative stress (OS) is the excitation of pressure intracellular signalling pathways caused by an oxidation imbalance in the generation and embodiment of reactive oxygen compounds (ROS), obviously public fringe groups, and also the ability of a living process, i.e. the antioxidative defense system is a system, to eliminate the harmful intermediates or to repair the resulting damage (Evans et al., 2002). Indications like this point to a potential involvement for oxidative stress in the progression of diabetes. Increased production of reactive oxygen substances, which may trigger a cascade of damaging effects by reacting with proteins, lipids, and polynucleotides, has been linked to cellular malfunction. There are several diseases in which an excess in free radical production contributes to tissue damage, including type 2 diabetes (Yildiz et al., 2002). Oxygen molecules radicals may alter the structure and function of proteins, mutate DNA, and peroxidize lipids inside the cell membrane via their interactions with these macromolecules. Lipid peroxidation, caused by free-radical activity, is a crucial factor in the worsening of diabetes complications. Due to the exposure of triglycerides in cell membranes, T2DM causes cell damage. Increased vulnerability to lipid peroxidation results from its degradation. Very high levels of free radicals contribute to the progression of diabetic complications by inducing lipid peroxidation, boosting insulin resistance, and damaging cellular organelles and enzymes. Toxic persistent aldehydes, such malondialdehyde, are produced when ROS degrade polyunsaturated triglycerides on cell membranes. This aldehyde product may be used as a biomarker to determine how much OS is present in a specific organism since it serves as a marker for OS. Despite evidence for an association between free radical activity and increased lipid peroxidation in type 1 and type 2 diabetes (Griesmacher et al., 1995; Jennings PE et al., 1991). Yet, despite a huge body of study, an elevation in oxidative damage in diabetes patients has not been found. This may be related to the heterogeneity of the patient population (Velazquez et al., 1991). It's worth noting that now the researchers themselves stressed the need of doing more studies to confirm the findings of this one. Weight problems are a leading cause of type 2 diabetes. White adiposity (WAT) is known to control numerous metabolic and endocrine processes [4, 5].

The WAT is a site of intense rivalry among M1 and M2 macrophages, as measured by their cytokine release [5]. A M2 profile helps reduce inflammation and metabolic syndrome [5, 6], whereas an M1 profile raises them. The anti-inflammatory protein adiponectin enhances insulin sensitivity and protects beta cells inside the pancreatic islets [6]. To do this, it boosts levels of the IL-1 receptor antagonist and blocks TNF-alpha naturally (IL-1Ra). Evidence suggests an inverse connection between adiponectin and visceral fat, and its levels are reduced in obese diabetic and cardiovascular disease patients [6]. This may explain why the abdominal fat of lean people is anti-inflammatory whereas that of obese folks is inflammatory [5]; the WAT may release IL-6 to change the equilibrium towards an M1 or M2 profile. Increased chemoattractant signals in WAT of obese people also serve to draw inflammatory responses to the tissues. Specifically, adipocytes secrete a signalling molecule termed monocyte chemotactic protein 1 (MCP-1) that regulates the distribution of monocytes [7].

T cells, macrophages, lymphocytes, and other immune cells, some of which may have Th1, Th2, and Th17 profiles, are all found in the WAT [8]. For example, there is a correlation between obesity and a decrease of Regulatory t cells lymphocytes [8]. The immune system may be modulated by anti-inflammatory molecules such il-1 (IL-10), interleukin-33 (IL-33), and transcription factor supporter of terrorism receptor gamma (PPAR gamma) [8]. It's possible that lymphocytes maintain a proinflammatory profile continuing [8]. As a result of obesity, irritation, and insulin resistance, M1 macrophages [8] produce more IL-17, TNF-alpha, and IL-1beta, ensuring that this metabolic imbalance continues. Allowing this inflammatory situation to remain will increase free fatty acids in circulation and reduce triglyceride deposition [8]. This creates oxidative phosphorylation problems, which in turn produce insulin resistance and impaired insulin-mediated glucose absorption. [12].

Increased production of PAI-1, stromal factor, thrombin, and factor VIII via these pathways generates a procoagulant state [12]. Thrombin inhibition type 1 (PAI-1) is linked to endothelial function, and also to proatherosclerotic & prothrombic changes, making it one of the first detectable markers of insulin resistance [14]. Indirect assessments of insulin sensitivity and obesity make the correlation between this factor and diabetes development indisputable. Glucose intolerance is useful in the early stages of prediabetes detection but becomes less so as the condition advances.

Interleukin-6 (IL-6) induces an inflammatory response known as the acute phase, which is heavily influenced by C-reactive protein (CRP) [15]. Hyperglycemia biomarkers, including C-reactive protein (CRP), are considered to be strong indicators of poorly controlled diabetes [17]. Microalbuminuria is associated with endothelial activation [18]

Increased risk of getting type 2 diabetes due to insulin resistance and impaired -cell activity brought on by elevated IL-1 beta levels [21]. IL-6 [18], a characteristic of the natural immune system reaction of type 2 diabetes, induces inflammation by increasing CRP production in the liver. Elevated IL-6 levels have been associated to increased production of symptomatic proteins, insulin resistance, including decreased tolerance to glucose (IGT) [20]. After controlling for body mass index and fasting insulin, the significance of CRP and IL-6 in the identification of T2DM is double. [18].

Glycation Biomarkers
The importance of an early diagnosis has been emphasised by the growth of research into phase-specific connections. Increased risk of prediabetes has been linked to higher EN-RAGE levels, whereas reduced risk of prediabetes, diabetes, and insulin dependence has been linked to increased IL-13 levels [3, 4]. Rapid progression form glycaemia to T2DM [22] was associated with both increased ICAM and VCAM levels, which were independent risk factors.

Mast cells, hematopoietic, leukocytosis, and Th2 lymphocytes all release IL-13, which inhibits immunodiabetogenic processes in the body [23]. Studies in animals have shown that IL-13 is essential for normal blood glucose in the hepatic, making this an important subject for further research [24].

As a pro-inflammatory granulocyte product [3], EN-RAGE has been proposed as a diagnostic for incident heart failure.

Microvascular T2DM complications
Microvascular disease in type 2 diabetes is often organ-specific. Indicators of renal and retinal damage will be reviewed here.

TNF-alpha, a cell communication and immunological cell regulator mostly secreted by adipocytes, is found in higher concentrations in people with micro- or macroalbuminuric diabetes [28]. Patients with type 2 diabetes and microvascular issues have been reported to have lower concentrations of ICAM comparing to age-matched healthy people [30], despite suggestions that ICAM expression follows the progression of diabetic nephropathy [29]. VCAM-1, a second adhesion molecule, has also been related to microvascular complications of type 2 diabetes.

Increased levels of VCAM-1 are often seen in patients with albuminuria [29]. The progression of diabetic nephropathy has been linked to both VCAM and ICAM, although VCAM has been shown to be more precise than ICAM, which just depicts systemic inflammation, in many investigations. [31].

Macrovascular T2DM complications
An increasing number of studies are looking at the use of biochemical markers in T2DM detection, and as a result, indicators of cardiovascular biological stress, venous renovating, and limited inflammatory, such as serum levels (NPs), galectin-3 (Gal-3), interleukins, and economic expansion differentiation factor-15 (GDF-15), are being addressed in light of their clinical utility [35, 36, 37]. Some researchers have even proposed using these markers to diagnose diabetes or predict patients' health outcomes in the future. [37].

Many cellular types have abundant Gal-3 lectin on their surfaces [48]. Soluble beta-galactosidebinding proteins include Gal-3. It regulates cellular collaboration, immunology, and extracellular interactions and has a significant impact on inflammation, clotting, thrombosis, and cancer [35]. Recent studies [35, 41] show that Gal-3 might serve as a helpful unbiased biomarker of vasculature remodelling and endothelium dysfunction associated with inflammatory proliferation, and atherosclerosis. Gal-3 was considered a potential predictor of coronary sclerosis in diabetics [40]. When present in high concentrations in the blood, Gal-3 has been related to an elevated chance of developing heart failure (HF), type 2 diabetes, and cardiovascular mortality rate in those with preexisting CV disorders [40, 41]. While Gal-3 has been found to predict cardiovascular prognosis in other patient groups, such is yet to be shown in patients with HF. [42].

Nevertheless, Gal-3 has not shown to be better to other markers like CRP, NPs, soluble regulation of tumorigenesis 2 (ST2), or growing differentiating factor 15 in predicting vasculopathy, decreased renal functioning, or CV mortality in individuals with T2DM [43]. (GDF- 15). In spite of this, there is mounting evidence that Gal-3 might be a potential treatment for persons without type 2 diabetes today. [41].

Table 1: Mean values of serum lipids, BMI, WC in study groups

Parameters	Type 2 DM poor metabolic control	Type 2 DM good metabolic control	Normal controls
HbA1c %	7.49±0.8	5.64±0.48	5.05±0.60
TC (mg/dl)	243.24±35.31	184.56±30.60	162.32±20.80
TG (mg/dl)	150.14±41.25	111.62±37.97	77.46±24.57
LDL (mg/dl)	147.99±36.58	102.69±28.88	79.54±32.13
VLDL (mg/dl)	31.22±8.53	26.14±7.48	15.72±4.97
HDL (mg/dl)	41.02±13.10	59.54±12.60	69.42±11.88
BMI (kg/m²)	26.53±1.89	23.40±1.52	21.92±1.34
Male WC (cm)	91.09±3.56	92.68±1.87	89.99±2.01
Female WC (cm)	90.87±5.04	82.85±2.65	79.22±2.13

TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, HbA1c: Glycosylated hemoglobin, LDL: Low-density lipoprotein, DM: Diabetes mellitus, BMI: Body mass index, WC: Waist circumference

Conclusion

Over the past several years, research on biomarkers and surrogate endpoints has flourished thanks to a deeper knowledge of the biology and genetics of obesity and its associated characteristics, such as CVDs. Obesity-related systems that are linked to the aforementioned biomarkers include inflammation, oxidative stress, adipokines' physiology, and nutritional regulation. The intricacy of the networks involved in the identification, treatment, and monitoring of these characteristics poses a barrier to the confirmation of these biomolecules as just a risk, diagnosing, and/or prognostic biomarker. Obesity and CVDs may be impacted by genetic abnormalities; therefore studying the molecular regulatory pathways involved in their development may have implications for their prevention, early identification, and treatment. Last but not least, understanding the mechanisms behind the initiation of inflammation and oxidative stress, as well as their biological importance and potential therapeutic implications, would provide consistent benefits for the efficient control, management, and management of obesity and CVDs.

References

[1] Weber K, Nowotny B, Strassburger K, Pacini G, Müssig K, Szendroedi J, et al. The Role of Markers of Low-Grade Inflammation for the Early Time Course of Glycemic Control, Glucose Disappearance Rate, and β-Cell Function in Recently Diagnosed Type 1 and Type 2 Diabetes. Diabetes Care. 2015; 38(9):1758-1767. Doi:10.2337/dc15-0169

[2] Brahimaj A, Ligthart S, Ikram M, Hofman A, Franco O, Sijbrands E, et al. Serum Levels of Apolipoproteins and Incident Type 2 Diabetes: A Prospective Cohort Study. Diabetes Care. 2016; 40(3):346-351. Doi:10.2337/dc16-1295

[3] Brahimaj A, Ligthart S, Ghanbari M, Ikram M, Hofman A, Franco O, et al. Novel inflammatory markers for incident pre-diabetes and type 2 diabetes: the Rotterdam Study. European Journal of Epidemiology. 2017; 32(3):217-226. Doi:10.1007/s10654-017-0236-0

[4] Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-Reactive Protein Levels in Overweight and Obese Adults. JAMA. 1999; 282(22):2131-2135.

[5] Stepien M, Stepien A, Wlazel R, Paradowski M, Banach M, Rysz J. Obesity indices and inflammatory markers in obese non-diabetic normo- and hypertensive patients. a comparative pilot study. Atherosclerosis. 2014; 235(2):e136-e137. Doi:10.1186/1476-511X-13-29

[6] Matsuzawa Y. Adiponectin: Identification, physiology and clinical relevance in metabolic and vascular disease. Atherosclerosis

Supplements. 2005; 6(2):7-14. Doi:10.1016/j.atherosclerosissup.2005.02.003

[7] Herder C, Baumert J, Thorand B, Koenig W, de Jager W, Meisinger C et al. Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg study, 1984–2002. Diabetologia. 2006; 49(5):921-929. Doi:10.1007/s00125-006-0190-y

[8] Pirola L, Ferraz J. Role of pro- and anti-inflammatory phenomena in the physiopathology of type 2 diabetes and obesity. World Journal of Biological Chemistry. 2017; 8(2):120-128. Doi:10.4331/wjbc.v8.i2.120

[9] Beringer A, Noack M, Miossec P. IL-17 in Chronic Inflammation: From Discovery to Targeting. Trends in Molecular Medicine. 2016; 22(3):230-241. Doi:10.1016/j.molmed.2016.01.001

[10] Chen C, Shao Y. Elevated Interleukin-17 Levels in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. Biochemistry & Physiology: Open Access. 2016; 5(2).

[11] Afzal N, Javaid K, Sami W, Zafar A, Jahan S, Zaman S, et al. Inverse Relationship of Serum IL-17 with Type-II Diabetes Retinopathy. Clinical Laboratory. 2013; 59(11-12)1311-1317.

[12] Guilherme A, Virbasius J, Puri V, Czech M. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nature Reviews Molecular Cell Biology. 2008; 9(5):367-377. Doi:10.1038/nrm2391

[13] Reddy S, Amutha A, Rajalakshmi R, Bhaskaran R, Monickaraj F, Rangasamy S et al. Association of increased levels of MCP-1 and cathepsin-D in young onset type 2 diabetes patients (T2DM-Y) with severity of diabetic retinopathy. Journal of Diabetes and its Complications. 2017; 31(5):804-809. Doi:10.1016/j.jdiacomp.2017.02.017

[14] Goldberg R. Cytokine and Cytokine-Like Inflammation Markers, Endothelial Dysfunction, and Imbalanced Coagulation in Development of Diabetes and Its Complications. The Journal of Clinical Endocrinology & Metabolism. 2009; 94(9):3171-3182. Doi:10.1210/jc.2008-2534

[15] Libby P, Ridker P. Inflammation and atherosclerosis: role of C-Reactive protein in risk assessment. The American Journal of Medicine. 2004; 116(6):9-16. Doi:10.1016/j.amjmed.2004.02.006

[16] Derosa G, Maffioli P. A review about biomarkers for the investigation of vascular function and impairment in diabetes mellitus. Vascular Health and Risk Management. 2016; 12:415-419. Doi:10.2147/VHRM.S64460

[17] Schölin A, Siegbahn A, Lind L, Berne C, Sundkvist G, Björk E et al. CRP and IL-6 concentrations are associated with poor glycemic control despite preservedβ-cell function during the first year after diagnosis of type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2004; 20(3):205-210. Doi:10.1002/dmrr.427

[18] Pradhan A, Manson JE, Rifai N, Buring JE, Ridker PM. C-Reactive Protein, Interleukin 6, and Risk of Developing Type 2 Diabetes Mellitus. JAMA. 2001; 286(3):327-334.

[19] Bhowmick K, Kutty A, Shetty H. Glycemic control modifies the association between microalbuminuria and c-reactive protein in Type 2 Diabetes Mellitus. Indian Journal of Clinical Biochemistry. 2007; 22(2):53-59. Doi:10.1007/BF02913314

[20] Müller S, Martin S, Koenig W, Hanifi-Moghaddam P, Rathmann W, Haastert B, et al. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-α or its receptors. Diabetologia. 2002; 45(6):805-812. Doi:10.1007/s00125-002-0829-2

[21] Ballak D, Stienstra R, Tack C, Dinarello C, van Diepen J. IL-1 family members in the pathogenesis and treatment of metabolic disease: Focus on adipose tissue inflammation and insulin resistance. Cytokine. 2015; 75(2):280-290. Doi:10.1016/j.cyto.2015.05.005

[22] Kulkarni H, Mamtani M, Peralta J, Almeida M, Dyer T, Goring H et al. Soluble Forms of Intercellular and Vascular Cell Adhesion Molecules Independently Predict Progression to Type 2 Diabetes in Mexican American Families. PLOS ONE. 2016; 11(3):e0151177. Doi:10.1371/journal.pone.0151177

[23] Mosmann T, Coffman R. Two types of mouse helper T-cell clone. Immunology Today. 1987; 8(7-8):223-227.

[24] Stanya K, Jacobi D, Liu S, Bhargava P, Dai L, Gangl M et al. Direct control of hepatic glucose

production by interleukin-13 in mice. Journal of Clinical Investigation. 2012; 123(1):261-271. Doi:10.1172/JCI64941

[25] Sumarac-Dumanovic M, Jeremic D, Pantovic A, Janjetovic K, Stamenkovic-Pejkovic D, Cvijovic G et al. Therapeutic improvement of glucoregulation in newly diagnosed type 2 diabetes patients is associated with a reduction of IL-17 levels. Immunobiology. 2013; 218(8):1113-1118. Doi:10.1016/j.imbio.2013.03.002

[26] Pan A, Wang Y, Yuan J, Koh W. High-sensitive C-reactive protein and risk of incident type 2 diabetes: a case–control study nested within the Singapore Chinese Health Study. BMC Endocrine Disorders. 2017; 17(1):8. Doi:10.1186/s12902-017-0159-5

[27] de Jager J, Dekker JM, Kooy A, Kostense PJ, Nijpels G, Heine RJ, et al. Endothelial Dysfunction and Low-Grade Inflammation Explain Much of the Excess Cardiovascular Mortality in Individuals With Type 2 Diabetes: The Hoorn Study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2006; 26(5):1086-1093. Doi:10.1161/01.ATV.0000215951.36219.a4

[28] Chen Y, Qiao Y, Xu Y, Ling W, Pan Y, Huang Y et al. Serum TNF-α concentrations in type 2 diabetes mellitus patients and diabetic nephropathy patients: A systematic review and meta-analysis. Immunology Letters. 2017; 186:52-58. Doi:10.1016/j.imlet.2017.04.003

[29] Luis-Rodríguez D. Pathophysiological role and therapeutic implications of inflammation in diabetic nephropathy. World Journal of Diabetes. 2012; 3(1):7-18. Doi:10.4239/wjd.v3.i1.7

[30] Hocaoglu-Emre F, Saribal D, Yenmis G, Guvenen G. Vascular Cell Adhesion Molecule 1, Intercellular Adhesion Molecule 1, and Cluster of Differentiation 146 Levels in Patients with Type 2 Diabetes with Complications. Endocrinology and Metabolism. 2017; 32(1):99-105. Doi:10.3803/EnM.2017.32.1.99

[31] Liu J, Yeoh L, Sum C, Tavintharan S, Ng X, Liu S et al. Vascular cell adhesion molecule-1, but not intercellular adhesion molecule-1, is associated with diabetic kidney disease in Asians with type 2 diabetes. Journal of Diabetes and its Complications. 2015; 29(5):707-712. Doi:10.1016/j.jdiacomp.2015.02.011

[32] Kato K, Osawa H, Ochi M, Kusunoki Y, Ebisui O, Ohno K et al. Serum total and high molecular weight adiponectin levels are correlated with the severity of diabetic retinopathy and nephropathy. Clinical Endocrinology. 2008; 68(3):442-449. Doi:10.1111/j.1365-2265.2007.03063.x

[33] Ersanli D, Top C, Öncül O, Aydin A, Terekeci H. Relationship between serum soluble E-selectin levels and development of diabetic retinopathy in patients with type 2 diabetes. Scandinavian Journal of Clinical and Laboratory Investigation. 2007; 67(5):474-479. Doi:10.1080/00365510601110148

[34] Nowak C, Sundström J, Gustafsson S, Giedraitis V, Lind L, Ingelsson E et al. Protein biomarkers for insulin resistance and type 2 diabetes risk in two large community cohorts. Diabetes. 2016; 65(1):276-284. Doi : 10.2337/db15-0881

[35] Berezin A. The Rationality to Use of Galectin-3 as Target in Biomarker-Guided Therapy of Type 2 Diabetes Mellitus. Endocrinology & Metabolic Syndrome. 2016; 05(01).

[36] Moro C. Targeting cardiac natriuretic peptides in the therapy of diabetes and obesity. Expert Opinion on Therapeutic Targets. 2016; 20(12):1445-1452. Doi:10.1080/14728222.2016.1254198

[37] E Berezin A. Cardiovascular Biomarkers in Routine Screening of Diabetic Patients. Clinical & Medical Biochemistry: Open Access. 2015; 01(01).

[38] Correction to: 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2016; 134(13):e298-e298. Doi:10.1161/CIR.0000000000000435

[39] Seferović P. ESC/HFA Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016. Journal of Cardiac Failure. 2017; 23(10):S7. Doi:10.1016/j.cardfail.2017.08.005

[40] Ozturk D, Celik O, Satilmis S, Aslan S, Erturk M, Cakmak H et al. Association between serum galectin-3 levels and coronary atherosclerosis and plaque burden/structure in patients with type 2 diabetes mellitus. Coronary Artery Disease. 2015; 26(5):396-401. Doi:10.1097/MCA.0000000000000252

[41] Shah R, Januzzi J. Soluble ST2 and Galectin-3 in Heart Failure. Clinics in Laboratory Medicine. 2014; 34(1):87-97. Doi:10.1016/j.cll.2013.11.009

[42] Coburn E, Frishman W. Comprehensive Review of the Prognostic Value of Galectin-3 in Heart Failure. Cardiology in Review. 2014; 22(4):171-175. Doi:10.1097/CRD.0000000000000013

[43] Alonso N, Lupón J, Barallat J, de Antonio M, Domingo M, Zamora E et al. Impact of diabetes on the predictive value of heart failure biomarkers. Cardiovascular Diabetology. 2016; 15(1):151. Doi:10.1186/s12933-016-0470-x

[44] Scirica B, Bhatt D, Braunwald E, Raz I, Cavender M, Im K et al. Prognostic Implications of Biomarker Assessments in Patients With Type 2 Diabetes at High Cardiovascular Risk. JAMA Cardiology. 2016; 1(9):989-998. Doi:10.1001/jamacardio.2016.3030

[45] Pareek M, Nielsen M, Leósdóttir M, Nilsson P, Olsen M. 4B.07. Journal of Hypertension. 2015; 33:e54-e55.

[46] Akoum N. New perspectives on atrial fibrillation and stroke. Heart. 2016; 102(22):1788-1792. Doi:10.1136/heartjnl-2015-309066

[47] McEvoy J, Lazo M, Chen Y, Shen L, Nambi V, Hoogeveen R et al. Patterns and determinants of temporal change in high-sensitivity cardiac troponin-T: The Atherosclerosis Risk in Communities Cohort Study. International Journal of Cardiology. 2015; 187:651-657. Doi:10.1016/j.ijcard.2015.03.436